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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/28/2003

Andrzej S. Krolewski

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EXAMINER

SITTON, JEHANNE SOUAYA

ART UNIT

PAPER NUMBER

1634

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

01/29/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/694,685

Applicant(s)

KROLEWSKI ET AL.

Examiner

Jehanne S. Sitton

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-54 is/are pending in the application.
- 4a) Of the above claim(s) 6-8, 10-21, 23-34, 37-46, 48, 51 and 53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-5, 9, 22, 35, 36, 47, 49, 50, 52 and 54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>2/04, 7/04, 10/05, 10/06</u> . | 6) <input checked="" type="checkbox"/> Other: <u>See Continuation Sheet</u> . |

Continuation of Attachment(s) 6). Other: Alignment of SEQ ID NO: 1142 of US Patent 6,979,557; Alignment of SEQ ID NO: 378 of US Patent 6,783,969.

DETAILED ACTION***Election/Restrictions***

1. Applicant's election with traverse, in part, of Group I, SEQ ID NO: 1, and SEQ ID NO: 16, in the reply filed on 10/30/2006 is acknowledged. The traversal is on the ground(s) that SEQ ID NOS: 1 is simply longer than SEQ ID NO: 3 and that SEQ ID O: 15 and 16 only differ by a single nucleotide. These arguments have been thoroughly reviewed. The restriction requirement between SEQ ID NOS 1 and 3 has been changed to an election of species. As the claims are not limited to simply SEQ ID NO: 1 or SEQ ID NO: 3, but include oligomers, as well as sequences with particular % identity, search results for SEQ ID NO: 1 would not necessarily provide results for SEQ ID NO: 3. Accordingly, as a proper search for claims directed to SEQ ID NO: 1 is not coextensive with the search required for SEQ ID NO: 3, the restriction requirement between them has been changed to an election of species. SEQ ID NO: 1 is considered the species elected. With regard to SEQ ID NOS 15 and 16, as the sequences are different, and require a different nucleotide at the indicated position in claims 8 and 9, the searches for each are different. Therefore, the restriction requirement has also been changed to an election of species and SEQ ID NO: 16 is considered the species elected.

2. Claim 1 is generic to the following disclosed patentably distinct species: SEQ ID NOS 1 and 3. The species are independent or distinct because they are structurally distinct nucleic acid molecules. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

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3. This application contains claims directed to the following patentably distinct species: SEQ ID NOS 15 and 16. The species are independent or distinct because they are structurally different nucleic acid molecules. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, no claim is generic.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The remainder of the restriction requirement other than the change to an election of species for SEQ ID NOS: 1/3 and 15/16, is deemed proper and made final.

4. Claims 8, 46, 48, 51, and 53 have been withdrawn from consideration as being drawn to non elected species. Claims 6-7, 10-21, 23-34, and 37-45 are withdrawn from consideration as being drawn to non elected inventions. An action on the merits of claims 1-5, 9, 22, 35, 36, 47, 49, 50, 52, and 54, directed to T2DM1, SEQ ID NO: 1, and 16 follows.

Specification

5. The disclosure is objected to because of the following informalities: the brief description to the drawings for figure 9A-MM does not include a sequence identifier for the sequence in the figure. The figure description should be amended to reflect the sequence identifier in the figure.

Appropriate correction is required.

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6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See for example, page 24, lines 24 which contains an active hyperlink.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-5, 9, 22, 35, 36, 47, 49, 50, 52, and 54 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

The claimed nucleic acids, vectors, host cells, and arrays are not supported by a specific asserted utility because the disclosed uses of the nucleic acids are not specific and are generally applicable to any nucleic acid. The specification states that the nucleic acid compounds may be used to express a polypeptide, to identify identical, similar or related polynucleotides, in screening assays, in diagnostic assays (page 64), and to determine expression levels. The specification further states that the nucleic acids can be used as probes for detecting identical or related sequences. However, these are non-specific uses that are applicable to nucleic acids in general and not particular or specific to the nucleic acid being claimed.

Further, the claimed nucleic acids, vectors, host cells, and methods of making and using the nucleic acids are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. For example, a nucleic acid may be utilized to obtain

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a protein. The protein could then be used in conducting research to functionally characterize the protein. The need for such research clearly indicates that the protein and/or its function is not disclosed as to a currently available or substantial utility. A starting material that can only be used to produce a final product does not have substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case, none of the proteins that are to be produced as final products resulting from processes involving claimed nucleic acids have specific and substantial utilities. The research contemplated by applicant(s) to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a "real world" context or use. Similarly, the other listed and asserted utilities as summarized above or in the instant specification are neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the nucleic acid and/or protein compound(s) such that another non-asserted utility would be well established for the compounds.

Although the specification asserts that the nucleic acids and polymorphisms can be used in diagnostic and prognostic assays (page 29), other than teaching the presence of 14 polymorphisms, and teaching that they were found in only 16 chromosomes of 8 type 2 diabetic patients, the specification provides no guidance as to whether the variants themselves are actually associated with type 2 diabetes, or whether the presence of these polymorphisms in diabetic subjects was due to chance. The specification does not teach the allele frequency of these polymorphisms in the normal population, in different racial/ethnic populations, nor does it

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teach how many patients were found to have each SNP. Accordingly, it is not predictable, given the limited information in the specification, whether these SNPs or polymorphisms would be expected to be found in the normal as well as type 2 diabetic population. The specification provides insufficient guidance to enable the skilled artisan to use the polymorphisms disclosed as a diagnostic or a marker for type 2 diabetes or any other disease.

Further, although the specification teaches that a BLASTp search was performed for the polypeptide of SEQ ID NO: 2 and was found to share homology with human Diff40, a search revealed, that the homology shared between SEQ ID NO: 2 and human Diff40 was only 35%. The specification also teaches that "T2DM1" is 27.4% identical to the human homolog of the mouse FOSB gene, and 26.3% identical to mouse SEM6C. However, these molecules are all structurally and functionally different, such that the identification of a specific % identity does not provide sufficient guidance to the skilled artisan to be able to reasonably confirm the function of SEQ ID NO: 2, or the nucleic acid encoding it, without further experimentation to actually characterize their functions. As noted by *Brenner v. Manson*, 383 US 519, 535-536 (1996), "Congress intended that no patents be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use - testing... a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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10. Claims 1-5, 9, 22, 35, 36, 47, 49, 50, 52, and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making an isolated nucleic acid molecule comprising SEQ ID NO: 1 or SEQ ID NO: 16, or an isolated nucleic acid molecule encoding SEQ ID NO: 2, as well as a purified host cell comprising a vector comprising an isolated nucleic acid molecule comprising SEQ ID NO: 1 or SEQ ID NO: 16, or an isolated nucleic acid molecule encoding SEQ ID NO: 2, does not reasonably provide enablement for using such nucleic acids or for making or using the nucleic acids or compositions encompassed by the broad scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Further, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims:

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Claims 1-5, 35, 36, 47, and 52 are drawn to isolated nucleic acids which have at least 95% identity to SEQ ID NO: 1, or encode a polypeptide with 95% identity to SEQ ID NO: 2, or which have at least 70% complementarity to a "T2DM1" nucleic acid or nucleic acids capable of detecting a "T2DM1" nucleic acid. The claims (claims 9, 22) are further drawn to sequences which comprise 15 or 20 contiguous nucleotides of SEQ ID NO: 1 or 16, as well as sequences which are only structurally defined by their ability to hybridize to SEQ ID NO: 1 under conditions of high stringency (claims 1, 49, 50). The claims also encompass a nucleic acid molecule comprising SEQ ID NO: 1 as well as SEQ ID NO: 16, and a nucleic acid molecule encoding SEQ ID NO: 2

The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology' (Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The amount of direction or guidance and presence and absence of working examples:

These claims represent an extremely large genus of allelic variants, mutants, and homologs of SEQ ID NO: 1 from any source. The specification teaches the sequence of the long form of T2DM1: SEQ ID NO: 1, the short form: SEQ ID NO: 3, as well as short fragments containing 14 polymorphisms that were found in T2DM1. However, the specification does not define the structural and functional attributes that a sequence is required to possess for the skilled artisan to be able to predictably determine what is a "T2DM1" nucleic acid vs not. The function of these sequences is not taught. Therefore, one of skill in the art would not be able to determine if a sequence was a T2DM1 sequence other than by SEQ ID NO:.

The specification teaches that a BLASTp search was performed for the polypeptide of SEQ ID NO: 2 and was found to share homology with human Diff40. However, a search revealed, that the homology shared between SEQ ID NO: 2 and human Diff40 was only 35%. The specification teaches that "T2DM1" is 27.4% identical to the human homolog of the mouse FOSB gene, and 26.3% identical to mouse SEM6C. However, these molecules are all structurally and functionally different, such that the identification of a specific % identity does not provide sufficient guidance to the skilled artisan to be able to determine the function of SEQ ID NO: 2.

The teachings in the specification indicate that the claimed invention is intended to encompass natural and non-natural variants, homologs, and orthologs, which have encode both functional and nonfunctional proteins (pages 39-40). The specification teaches 14 polymorphisms, however, the specification does not teach whether the disclosed polymorphisms alter the function of the encoded protein or not. The specification particularly does not identify any variants having similar, increased or decreased activity as compared to the polypeptide encoded by SEQ ID NO: 1 or SEQ ID NO: 3. The specification does not disclose any additional variants of the polypeptide encoded by SEQ ID NO: 2.

Preferred variants are asserted to be those correlated with susceptibility to type 2 diabetes (page 40, line 23). However, other than teaching the presence of 14 polymorphisms, and teaching that they were found in only 16 chromosomes of 8 type 2 diabetic patients, the specification provides no guidance as to whether the variants themselves are actually associated with type 2 diabetes, or whether the presence of these polymorphisms in diabetic subjects was due to chance. The specification does not teach the allele frequency of these polymorphisms in

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the normal population, in different racial/ethnic populations, nor does it teach how many patients were found to have each SNP. Accordingly, it is not predictable, given the limited information in the specification, whether these SNPs or polymorphisms would be expected to be found in the normal as well as type 2 diabetic population. The specification provides insufficient guidance to enable the skilled artisan to use the polymorphisms disclosed as a diagnostic or a marker for type 2 diabetes.

Further, the claims encompass host cells in vivo. The specification asserts the use of cells as pharmaceutical preparations in gene therapy, however, the specification does not provide any teaching or guidance regarding any therapy using the claimed nucleic acids or host cells. The specification provides no guidance on any particular therapy, routes or modes of administration, etc for one of skill in the art to predictably determine a therapeutic use or application for the claimed products.

The state of the prior art and the predictability or unpredictability of the art:

With regard to the teachings of alignments with other proteins, such evidence is not found to predictably establish the function of the polypeptide of SEQ ID NO: 2, as exemplified by the teachings of the prior art. For example, Fetrow teaches (Fetrow et al., J. Mol. Biol., vol. 282, pp 703-711, 1998) that although function prediction by homology to previously characterized proteins is extremely successful and is fast, cheap and reliable, there are several problems that limit its potential utility, one of which is that sequence homology does not guarantee functional similarity (p 704, col. 1, 1st full paragraph). Fetrow teaches that "threading"(analysis using structure prediction tools) can identify topological cousins, that is,

protein families such as the α/β barrels with similar structures, but dissimilar functions. Fetrow teaches using a three dimensional descriptor of the active site of a protein, termed "fuzzy functional form" (FFF) and argues that threading alone is not enough to provide the required information about function because it has been shown that pairs of proteins can have similar structures but unrelated functions (p. 706, col. 2, last para). Fetrow teaches that because such topological cousins exist, knowledge of the structure is not equivalent to identification of protein function. Skolnick (Skolnick and Fetrow, TIBTECH, January 2000, vol. 18, pp 34-39) teaches (p. 35, "Box 1") that a common protein characteristic that makes functional analysis based only on homology especially difficult is the tendency of proteins to be multifunctional. Skolnick teaches that for example, lactate dehydrogenase binds NAD, substrate, and zinc and performs a redox reaction and that each of these occurs at different functional sites that are in close proximity and the combination of all four sites creates the fully functional proteins. Skolnick also teaches that the serine threonine phosphatase superfamily is a prime example of the difficulties of using standard sequence analysis to recognize the multiple functions found in single proteins. Skolnick teaches that this large protein family is divided into a number of subfamilies, all of which contain an essential phosphatase active site. He teaches that subfamilies 1, 2A and 2b exhibit 40% or more sequence identity between them, however each of these subfamilies is apparently regulated differently by the cell and observation suggest that there are different functional sites at which regulation can occur. Skolnick teaches that because the sequence identity between subfamilies is so high, standard sequence similarity methods could easily misclassify new sequences as members of the wrong subfamily if the functional sites are not carefully considered. Further, it is noted that the degree of identity to each molecule set forth

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in the specification is low. Berendsen teaches (Berendsen, Science, vol. 282, pages 642-643, 1998) teaches that although homology modeling provides information regarding known structures, the methods are only effective for 25% of proteins for which the amino acid sequence is known, and that if homology drops below 25%, the reliability of database oriented methods drops to nearly zero. Therefore, the art specifically teaches, that sequence alignment alone does not necessarily provide a predictable correlation between the structure and specific function of a protein. Additionally, the function of each of the molecules disclosed in the specification is different, such that the disclosure of BLAST search results with low levels of homology does not provide the skilled artisan with a predictable function or readily apparent use for the claimed nucleic acid molecules. The teachings with regard to Diff40 at page 25 of the specification, do not provide the skilled artisan with any predictable function for SEQ ID NO: 2 or 4, nor does it provide any guidance as to the association of such proteins, the nucleic acids encoding them, or variants with regard to type 2 diabetes.

Although the specification teaches that the polymorphism in SEQ ID NO: 16 can be used in diagnostic and prognostic methods, as noted above, the specification does not provide any guidance as to whether the SNP disclosed in SEQ ID NO: 16, or any of the other SNPs, is associated with or a marker for type 2 diabetes. The detection of new polymorphisms is an entirely unpredictable art which is empirical in nature, and once these polymorphisms are detected, their association with a phenotype must be established before they can be used in any predictive manner. There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states, as well as drug or therapeutic response. However, the art is highly unpredictable with regard to the functionality of

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polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker et al. teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Hacker et al; Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β -globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789). Further, in some cases where multiple polymorphisms were identified in a gene, some of these were demonstrated to be disease associated and some were not. For example, Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma Blumenfeld et al found that some of these polymorphisms are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined not to have a statistical association with asthma ($p=0.294$). In the instant case, the specification only provides information that the variant exists, but provides no guidance that it has any effect or is associated with or is a marker for type 2 diabetes. Further, even if an association is demonstrated between a single polymorphism within a gene and a phenotype, it is

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not necessarily a predictor that a different polymorphism within a gene will also have the same predictive ability. In the instant case, as the specification does not teach if the polymorphisms alter the sequence of the encoded protein (SEQ ID NO: 2) and further because the specification does not teach the function of the protein, it is unpredictable as to whether any other polymorphism would have any phenotypic effect, let alone what that phenotypic effect might be. Additionally, in the instant invention, a high level complexity and unpredictability also exists in simply establishing that within a given combination of SNPs, differences observed with regard to phenotype are not due to chance alone, because no teaching of any statistically significant association is taught, nor does the specification provide any guidance as to the allele frequencies of each polymorphism in ethnically matched patients and normal controls. For example, it is unclear if there was a lack of statically significant results, and if so, if it was due to small sample size (see Nature Genetics, vol. 22, pages 1-2, 1999; "Freely Associating").

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

Given the lack of guidance in the specification and as exemplified by the teachings of the art, a large amount of unpredictable trial and error experimentation would be required of the skilled artisan to make and use the broadly claimed invention. The skilled artisan would first be required to determine the function of the claimed nucleic acids to determine if there was any association with type 2 diabetes. Additionally, the skilled artisan would be required to perform a

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large study of patients and ethnically matched controls to determine if the presence of the claimed polymorphism was diagnostic for, prognostic for, or a marker for type 2 diabetes or if the polymorphism also exists in the general population with similar allelic frequency. The experimentation required by the skilled artisan amounts to a research project with each of the intervening steps not being guaranteed of a successful or predictable result. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform make and use nucleic acids encompassed by the claims.

11. Claims 1-5, 9, 22, 35-36, 47, 49, 50, and 52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, 35, 36, 47, and 52 are drawn to isolated nucleic acids which have at least 95% identity to SEQ ID NO: 1, or encode a polypeptide with 95% identity to SEQ ID NO: 2, or which have at least 70% complementarity to a "T2DM1" nucleic acid or nucleic acids capable of detecting a "T2DM1" nucleic acid. The claims (claims 9, 22) are further drawn to sequences which comprise 15 or 20 contiguous nucleotides of SEQ ID NO: 1 or 16, as well as sequences

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which are only structurally defined by their ability to hybridize to SEQ ID NO: 1 under conditions of high stringency (claims 1, 49, 50). These claims represent an extremely large genus of allelic variants, mutants, and homologs of SEQ ID NO: 1 from any source. The specification teaches the sequence of the long form of T2DM1: SEQ ID NO: 1, the short form: SEQ ID NO: 3, as well as short fragments containing 14 polymorphisms that were found in T2DM1. However, the specification does not define the structural and functional attributes that a sequence is required to possess to be considered a "T2DM1" nucleic acid. The function of these sequences is not taught. Therefore, one of skill in the art would not be able to determine if a sequence was a T2DM1 sequence other than by SEQ ID NO:.

The specification teaches that a BLASTp search was performed for the polypeptide of SEQ ID NO: 2 and was found to share homology with human Diff40. However, a search revealed, that the homology shared between SEQ ID NO: 2 and human Diff40 was only 35%. The specification teaches that "T2DM1" is 27.4% identical to the human homolog of the mouse FOSB gene, and 26.3% identical to mouse SEM6C. However, these molecules are all structurally and functionally different, such that the identification of a specific % identity does not provide sufficient guidance to the skilled artisan to be able to determine the function of SEQ ID NO: 2. The teachings in the specification indicate that the claimed invention is intended to encompass natural and non-natural variants, homologs, and orthologs, which have encode both functional and nonfunctional proteins (pages 39-40). Preferred variants are asserted to be those correlated with susceptibility to type 2 diabetes. However, other than teaching the presence of 14 polymorphisms, and teaching that they were found in only 16 chromosomes of subjects with type 2 diabetes, the specification provides no guidance as to whether the variants themselves are

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actually correlated with type 2 diabetes, or are due to chance alone. The specification does not disclose any additional variants of the polypeptide encoded by SEQ ID NO: 2, nor does the specification teach whether the disclosed polymorphisms alter the function of the encoded protein or not. The specification particularly does not disclose any variants having similar, increased or decreased activity as compared to the polypeptide encoded by SEQ ID NO: 1 or SEQ ID NO: 3. Accordingly, while isolated polynucleotides comprising SEQ ID NO: 1, SEQ ID NO: 3, and consisting of SEQ ID NO: 16, as well as nucleic acids encoding the polypeptide of SEQ ID NO: 2 or 4, meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus of nucleic acid molecules encompassed by the broadly claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed”. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that “An adequate written description of a DNA...” requires a precise definition,

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such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the only members of the claimed genus of polynucleotides with the disclosed % identity or complementarity or ability to hybridize under conditions of high stringency to SEQ ID NO: 1 which have been defined in terms of structure, are SEQ ID NO: 1, SEQ ID NO: 3, and 14 polymorphisms.

It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., in terms of a specific functional activity). In the instant case, no such identifying characteristics have been provided for any additional variants. While one could contemplate a nucleic acid substitution, deletion or addition at each and every position in SEQ ID NO: 1, such alterations are not considered to be equivalent to specific naturally occurring variants, homologs and orthologs of the polypeptide encoded by SEQ ID NO: 1. Accordingly, knowledge of the sequence of SEQ ID NO: 1 and the putative amino acid sequence of SEQ ID NO: 2 does not allow the skilled artisan to envision all of the contemplated polymorphisms, functional variants, splice variants, homologs and orthologs encompassed by the claimed genus of polypeptides. Therefore, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

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12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 3-5 recite the term 'host' cell, however it is not clear if the claim intends it to encompass a host organism, such as an animal or not. From applicant's election of group I, distinct from the transgenic animal claims in group VII, it appears that the claim is intended to refer to a purified cell. It is suggested that the claims be amended to recite the term "purified" to clearly distinguish it from an animal.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1-5, 22, 35, 36, 47, 49, 50, 52 and 54 are rejected under 35 U.S.C. 102(e) as being anticipated by Tang (Tang et al; US Patent 6,783,969)

Tang teaches a nucleotide sequence which is 98% identical to the nucleotide sequence of SEQ ID NO: 1, and has 96.5% identity over the full length of SEQ ID NO: 1 (SEQ ID NO: 378 of Tang; alignment provided). Tang teaches vectors and host cells, including mammalian and

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human host cells comprising the sequence (col. 15, lines 10-30; col. 20, lines 36-55), sequences that hybridize to such under highly stringent conditions (col. 10, lines 33-40). Tang teaches primers and probes (col. 12, lines 40-44) as well as fragments of greater than 17 nucleotides (col. 13, line 1), arrays comprising oligomers (col. 31, lines 25-36), as well as compositions (col. 52, lines 55) and multiple antisense sequences (col. 30-lines 43-col. 31).

16. Claims 1, 35, 36, 47, and 52 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Fodor (US Pregrant Publication 20010053519).

Fodor teaches an array of all possible 10 mer nucleic acid sequences (example 2). The claims, for example claim 1, do not require that the recited % identity be over the full length of the molecule. The claims encompass a large genus of nucleic acid molecules which can have 70% (claim 36), or 95% (claim 1, claim 47) identity to SEQ ID NO: 1, as well as molecules which have no recited structural limitations (claim 35). The genus of nucleic acids taught by Fodor anticipates the genus of claimed nucleic acid molecules.

17. Claims 1, 35, 36, 47, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US Patent 5,474,796).

Brennan teaches an array of all possible 10 mer nucleic acid sequences (see cols 9-10). The claims, for example claim 1, do not require that the recited % identity be over the full length of the molecule. The claims encompass a large genus of nucleic acid molecules which can have 70% (claim 36), or 95% (claim 1, claim 47) identity to SEQ ID NO: 1, as well as molecules

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which have no recited structural limitations (claim 35). The genus of nucleic acids taught by Brennan anticipates the genus of claimed nucleic acid molecules.

18. Claims 1-4, 9, 22, 35-36, 47, 49-50, and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Isogai (Isogai et al; US Patent 6,979,557).

Isogai teaches an isolated nucleic acid molecule (SEQ ID NO: 1142) which comprises a nucleic sequence which is 100% identical to SEQ ID NO: 1 (alignment provided). Isogai teaches vectors and host cells, including mammalian host cells comprising the sequence (col. 33), sequences that hybridize to such under highly stringent conditions (col. 31, lines 1-5). Isogai teaches primers and probes (col. 12, lines 40-44) as well as fragments of greater than 15 nucleotides (col. 31, lines 63-67), arrays and compositions comprising nucleic acids (library), and multiple antisense sequences (col. 32, lines 39-45).

19. Claims 1-3, 22, 47, and 49-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Genbank Accession number BF688656 (Dec. 2000).

With regard to claims 1-3 and 47. Genbank Accession number BF688656 teaches a sequence which has 99.8% identity to SEQ ID NO: 1 (alignment provided). The sequence is taught to have been a clone and comprised in a vector, pOTB7, and in a host cell: DH10B. With regard to claim 22, the sequence comprises 15 nucleotides of SEQ ID NO: 1. With regard to claims 49-50, the T_m of the sequence is over 80 deg C and would be expected to hybridize under the conditions set forth in the claims.

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Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton

Jehanne Sitton
Primary Examiner
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1/18/07

Alignment for Sequence 1142 of US Patent
6,979,557

RESULT 2

US-10-094-749-1142/c

; Sequence 1142, Application US/10094749

; Publication No. US20030219741A1

; GENERAL INFORMATION:

; APPLICANT: ISOGAI, TAKAO

; APPLICANT: SUGIYAMA, TOMOYASU

; APPLICANT: OTSUKI, TETSUJI

; APPLICANT: WAKAMATSU, AI

; APPLICANT: SATO, HIROYUKI

; APPLICANT: ISHII, SHIZUKO

; APPLICANT: YAMAMOTO, JUN-ICHI

; APPLICANT: ISONO, YUUKO

; APPLICANT: HIO, YURI

; APPLICANT: OTSUKA, KAORU

; APPLICANT: NAGAI, KEIICHI

; APPLICANT: IRIE, RYOTARO

; APPLICANT: TAMECHIKA, ICHIRO

; APPLICANT: SEKI, NAOHIKO

; APPLICANT: YOSHIKAWA, TSUTOMU

; APPLICANT: OTSUKA, MOTUYUKI

; APPLICANT: NAGAHARI, KENJI

; APPLICANT: MASUHO, YASUHIKO

; TITLE OF INVENTION: NOVEL FULL-LENGTH cDNA

; FILE REFERENCE: 084335/0160

; CURRENT APPLICATION NUMBER: US/10/094,749

; CURRENT FILING DATE: 2002-03-12

; PRIOR APPLICATION NUMBER: 60/350,435

; PRIOR FILING DATE: 2002-01-24

; PRIOR APPLICATION NUMBER: JP 2001-328381

; PRIOR FILING DATE: 2001-09-14

; NUMBER OF SEQ ID NOS: 3381

; SOFTWARE: PatentIn Ver. 2.1

; SEQ ID NO 1142

; LENGTH: 2698

; TYPE: DNA

; ORGANISM: Homo sapiens

US-10-094-749-1142

Query Match 100.0%; Score 40; DB 7; Length 2698;

Best Local Similarity 100.0%; Pred. No. 4.7e-14;

Matches 40; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 AAACAGGGACAGCTCATCCGGGGCGAAGTCGGCATTGAGG 40

|||||

Db 2076 AAACAGGGACAGCTCATCCGGGGCGAAGTCGGCATTGAGG 2037

Alignment for Sequence 378 from US Patent 6,783,969

RESULT 1

AR578202

LOCUS AR578202 4449 bp DNA linear PAT 14-DEC-2004

DEFINITION Sequence 378 from patent US 6783969.

ACCESSION AR578202

VERSION AR578202.1 GI:56580998

KEYWORDS

SOURCE Unknown.

ORGANISM Unknown.

Unclassified.

REFERENCE 1 (bases 1 to 4449)

AUTHORS Tang, Y.T., Goodrich, R.W., Asundi, V. and Drmanac, R.T.

TITLE Cathepsin V-like polypeptides

JOURNAL Patent: US 6783969-A 378 31-AUG-2004;

Nuvelo, Inc.; Sunnyvale, CA

FEATURES Location/Qualifiers

source 1. .4449

/organism="unknown"

/mol_type="genomic DNA"

ORIGIN

Query Match 96.5%; Score 4063; DB 2; Length 4449;

Best Local Similarity 98.0%; Pred. No. 0;

Matches 4156; Conservative 0; Mismatches 0; Indels 83; Gaps 1;

Qy	56	GCCAGATAAGAGTCCCGGCTGCATTATCAGAGCCCGGCAGGGCACC	115
Db	107	GCCAGATAAGAGTCCCGGCTGCATTATCAGAGCCCGGCAGGGCACC	166
Qy	116	AGAAGGAAGACTCGGGGCGCAGCAGGTCTCAAGGCGATCTTCCCAGAGAGCGGGACCAG	175
Db	167	AGAAGGAAGACTCGGGGCGCAGCAGGTCTCAAGGCGATCTTCCCAGAGAGCGGGACCAG	226
Qy	176	CGGCTGGTGGCCAGTGTGGATGGAATTTGCAGAGCCCTAGCTCGAGTCCGGGAGTCCCGG	235
Db	227	CGGCTGGTGGCCAGTGTGGATGGAATTTGCAGAGCCCTAGCTCGAGTCCGGGAGTCCCGG	286
Qy	236	GCCAGATGGGAGCAGACGCTTGCTGGCGGCAATAGGGAAAGTGAGGCAGCTGCAAGGAGG	295
Db	287	GCCAGATGGGAGCAGACGCTTGCTGGCGGCAATAGGGAAAGTGAGGCAGCTGCAAGGAGG	346
Qy	296	GCGGCGGGACTGCACTCGAGTGTCCAGACCTGCTCGATGGTGACCACCATGTCCGGTGAGG	355
Db	347	GCGGCGGGACTGCACTCGAGTGTCCAGACCTGCTCGATGGTGACCACCATGTCCGGTGAGG	406
Qy	356	TTGCGGTTCTGTCCCTGGGGACACAGGGGCCGTGGGGGTCGTGGGCCGGAGCGCCTCC	415
Db	407	TTGCGGTTCTGTCCCTGGGGACACAGGGGCCGTGGGGGTCGTGGGCCGGAGCGCCTCC	466
Qy	416	TTGCGAGGCTTCAGCAGTGCACAGAGCCGGAGGATCGAAAGTCCATCAACAGGAAGTCC	475
Db	467	TTGCGAGGCTTCAGCAGTGCACAGAGCCGGAGGATCGAAAGTCCATCAACAGGAAGTCC	526
Qy	476	GTGAGATCGCGAATGCCTGCAAAATCCTCCAAGATGTACGGCACGCTGCGGAAGGGGTCG	535
Db	527	GTGAGATCGCGAATGCCTGCAAAATCCTCCAAGATGTACGGCACGCTGCGGAAGGGGTCG	586

Qy	536	GTCTGTGCAGACCCGAAGCCCCAGCAGGTGAAGAAGATCTTCGAAGCATTGAAAAGAGGC	595
Db	587	GTCTGTGCAGACCCGAAGCCCCAGCAGGTGAAGAAGATCTTCGAAGCATTGAAAAGAGGC	646
Qy	596	CTCAAGGAGTATCTGTGTGTGCAGCAGGCTGAGCTGGACCACCTGTCTGGACGCCACAAA	655
Db	647	CTCAAGGAGTATCTGTGTGTGCAGCAGGCTGAGCTGGACCACCTGTCTGGACGCCACAAA	706
Qy	656	GACACCAGGAGGAATTCCAGGCTGGCTTTCTATTATGACCTGGACAAGCAAACGCGCTGT	715
Db	707	GACACCAGGAGGAATTCCAGGCTGGCTTTCTATTATGACCTGGACAAGCAAACGCGCTGT	766
Qy	716	GTGGAAAGGCACATTTCGGAAGATGGAGTTTCACATCAGCAAGGTGGATGAGCTGTACGAG	775
Db	767	GTGGAAAGGCACATTTCGGAAGATGGAGTTTCACATCAGCAAGGTGGATGAGCTGTACGAG	826
Qy	776	GACTACTGCATCCAGTGCCGCCCTGCGCGACGGCGCCTCCAGCATGCAGCGGGCCTTCGCC	835
Db	827	GACTACTGCATCCAGTGCCGCCCTGCGCGACGGCGCCTCCAGCATGCAGCGGGCCTTCGCC	886
Qy	836	CGGTGCCCCCGAGCCGCGCAGCCCCGAGAGAGCCTGCAGGAGCTGGGCCGCGAGCCTGCAC	895
Db	887	CGGTGCCCCCGAGCCGCGCAGCCCCGAGAGAGCCTGCAGGAGCTGGGCCGCGAGCCTGCAC	946
Qy	896	GAGTGCGCCGAGGACATGTGGCTCATCGAGGGGGCCCTGGAGGTTACCTGGGCGAGTTC	955
Db	947	GAGTGCGCCGAGGACATGTGGCTCATCGAGGGGGCCCTGGAGGTTACCTGGGCGAGTTC	1006
Qy	956	CACATCAGGATGAAAGGCTTGGTGGGCTACGCACGCCTCTGTCCCGGAGACCACTATGAG	1015
Db	1007	CACATCAGGATGAAAGGCTTGGTGGGCTACGCACGCCTCTGTCCCGGAGACCACTATGAG	1066
Qy	1016	GTGCTCATGCGTCTGGGCCGCCAGCGTTGGAAGCTCAAGGGTTCGGATCGAGTCAGATGAC	1075
Db	1067	GTGCTCATGCGTCTGGGCCGCCAGCGTTGGAAGCTCAAGGGTTCGGATCGAGTCAGATGAC	1126
Qy	1076	AGCCAGACCTGGGACGAAGAGGAGAAGGCCTTCATCCCCACGCTGCATGAGAACCTGGAC	1135
Db	1127	AGCCAGACCTGGGACGAAGAGGAGAAGGCCTTCATCCCCACGCTGCATGAGAACCTGGAC	1186
Qy	1136	ATCAAGGTGACGGAGTTGCGGGGCCCTGGGCTCGCTGGCTGTGGGTGCAGTGACGTGTGAC	1195
Db	1187	ATCAAGGTGACGGAGTTGCGGGGCCCTGGGCTCGCTGGCTGTGGGTGCAGTGACGTGTGAC	1246
Qy	1196	ATCGCCGACTTCTTCACGACGCGGCCGAGGTCATCGTGGTGGACATCACGGAGTTGGGT	1255
Db	1247	ATCGCCGACTTCTTCACGACGCGGCCGAGGTCATCGTGGTGGACATCACGGAGTTGGGT	1306
Qy	1256	ACCATCAAGCTGCAGCTGGAGGTGCAGTGGAACCCGTTTGATACTGAGAGCTTCCTGGTG	1315
Db	1307	ACCATCAAGCTGCAGCTGGAGGTGCAGTGGAACCCGTTTGATACTGAGAGCTTCCTGGTG	1366
Qy	1316	TCACCCAGCCCCACGGGCAAGTTTTCTATGGGCAGCAGGAAGGGCTCCTTGTAACAACCTGG	1375
Db	1367	TCACCCAGCCCCACGGGCAAGTTTTCTATGGGCAGCAGGAAGGGCTCCTTGTAACAACCTGG	1426
Qy	1376	ACACCCCCGAGCACCCCCAGCTTCCGGGAGAGATACTACCTGTCTGTCTCTACAGCAGCCA	1435

Db	1427	 ACACCCCGAGCACCCCGAGCTTCCGGGAGAGATACTACCTGTCTGTCTTACAGCAGCCA	1486
Qy	1436	 ACACAGCAGGCCTTGCTGCTGGGTGGCCCAAGGGCCACCTCCATCCTCAGCTACCTGTCT	1495
Db	1487	 ACACAGCAGGCCTTGCTGCTGGGTGGCCCAAGGGCCACCTCCATCCTCAGCTACCTGTCT	1546
Qy	1496	 GACAGCGACCTCCGGGGTCCCAGCCTAAGAAGCCAGAGTCAGGAGCTGCCTGAGATGGAC	1555
Db	1547	 GACAGCGACCTCCGGGGTCCCAGCCTAAGAAGCCAGAGTCAGGAGCTGCCTGAGATGGAC	1606
Qy	1556	 TCCTTCAGCTCTGAGGACCCCCGAGACACGGAGACCAGCACGTCGGCGTCCACCTCAGAT	1615
Db	1607	 TCCTTCAGCTCTGAGGACCCCCGAGACACGGAGACCAGCACGTCGGCGTCCACCTCAGAT	1666
Qy	1616	 GTGGGCTTCCTGCCCTTGACCTTCGGTCCCCACGCCTCCATTGAAGAGGAGGCTCGGGAG	1675
Db	1667	 GTGGGCTTCCTGCCCTTGACCTTCGGTCCCCACGCCTCCATTGAAGAGGAGGCTCGGGAG	1726
Qy	1676	 GACCCCTGCCCCAGGTCTCCTGCCAGAGATGGCCCACCTCTCTGGAGGCCCGTTTGCA	1735
Db	1727	 GACCCCTGCCCCAGGTCTCCTGCCAGAGATGGCCCACCTCTCTGGAGGCCCGTTTGCA	1786
Qy	1736	 GAGCAGCCTGGCTGGAGGAACCTTAGGAGGGGAGAGCCCCAGCCTGCCACAGGGCTCCCTG	1795
Db	1787	 GAGCAGCCTGGCTGGAGGAACCTTAGGAGGGGAGAGCCCCAGCCTGCCACAGGGCTCCCTG	1846
Qy	1796	 TTCCACAGCGGCACAGCCTCGAGTAGCCAGAACGGCCACGAGGAAGGGGCAACCGGGGAC	1855
Db	1847	 TTCCACAGCGGCACAGCCTCGAGTAGCCAGAACGGCCACGAGGAAGGGGCAACCGGGGAC	1906
Qy	1856	 AGAGAGGACGGGCCTGGCGTGGCCCTCGAGGGGCCTCTGCAGGAGGTCTGGAGTTGCTG	1915
Db	1907	 AGAGAGGACGGGCCTGGCGTGGCCCTCGAGGGGCCTCTGCAGGAGGTCTGGAGTTGCTG	1966
Qy	1916	 AGGCCCACGGACTCCACCCAGCCCCAGCTCCGGGAGCTGGAGTACCAGGTCCTCGGCTTC	1975
Db	1967	 AGGCCCACGGACTCCACCCAGCCCCAGCTCCGGGAGCTGGAGTACCAGGTCCTCGGCTTC	2026
Qy	1976	 CGGGACCGGCTGAAGCCCTGCAGAGCACGGCAGGAGCACACCTCGGCCGAGAGCCTGATG	2035
Db	2027	 CGGGACCGGCTGAAGCCCTGCAGAGCACGGCAGGAGCACACCTCGGCCGAGAGCCTGATG	2086
Qy	2036	 GAGTGCATCCTGGAGAGCTTCGCCTTCCTCAATGCCGACTTCGCCCTGGATGAGCTGTCC	2095
Db	2087	 GAGTGCATCCTGGAGAGCTTCGCCTTCCTCAATGCCGACTTCGCCCTGGATGAGCTGTCC	2146
Qy	2096	 CTGTTTGGGGGCTCCCAGGGTCTCCGAAAGGACCGGCCCCTGCCCCACCGTCATCACTG	2155
Db	2147	 CTGTTTGGGGGCTCCCAGGGTCTCCGAAAGGACCGGCCCCTGCCCCACCGTCATCACTG	2206
Qy	2156	 AAAGCGTCATCCAGGGAACCTCACAGCCGGTGCCCCAGAGCTGGACGTGCTGCTGATGGTA	2215
Db	2207	 AAAGCGTCATCCAGGGAACCTCACAGCCGGTGCCCCAGAGCTGGACGTGCTGCTGATGGTA	2266
Qy	2216	 CACCTCCAAGTCTGCAAAGCTCTGCTGCAGAAACTGGCCTCCCCTAATTTATCAAGGCTG	2275

Db	2267	CACCTCCAAGTCTGCAAAGCTCTGCTGCAGAAACTGGCCTCCCCTAATTTATCAAGGCTG	2326
Qy	2276	GTCCAGGAATGCCTCCTGGAAGAAGTGGCACAGCAAAAGCACGTTCTGGAGACACTTTCT	2335
Db	2327	GTCCAGGAATGCCTCCTGGAAGAAGTGGCACAGCAAAAGCACGTTCTGGAGACACTTTCT	2386
Qy	2336	GTCCTTGACTTTGAGAAGGTCGGCAAGGCAACATCCATTGAAGAGA-----	2381
Db	2387	GTCCTTGACTTTGAGAAGGTCGGCAAGGCAACATCCATTGAAGAGAGTCCTAGTGGAGGG	2446
Qy	2382	-----	2381
Db	2447	AAACCTTTCGGGTCCTTGTTCATGTGCTCTCCCCGAGTCACCATTTCAGGTTTCTGAAC TGG	2506
Qy	2382	-----TCATCCACAGGCCTCGCGGACGAAGGGGTGCCTGAAGCTGTGGAGAGGGT	2432
Db	2507	GGCTTTTCAGTCATCCACAGGCCTCGCGGACGAAGGGGTGCCTGAAGCTGTGGAGAGGGT	2566
Qy	2433	GCACAGGGCCTGGCAGGGTCCTGTCTGCCCTGCCACGACGCTGCTGAACCAGCTCAAGA	2492
Db	2567	GCACAGGGCCTGGCAGGGTCCTGTCTGCCCTGCCACGACGCTGCTGAACCAGCTCAAGA	2626
Qy	2493	AAACCTTCCAGCACAGAGTCAGAGGGAAGTACCCAGGACAGCTGGAAATAGCGTGCCGCA	2552
Db	2627	AAACCTTCCAGCACAGAGTCAGAGGGAAGTACCCAGGACAGCTGGAAATAGCGTGCCGCA	2686
Qy	2553	GGCTCCTGGAGCAGGTGGTCAGCTGTGGTGGGCTGCTCCCCGGAGCTGGGCTCCCAGAAG	2612
Db	2687	GGCTCCTGGAGCAGGTGGTCAGCTGTGGTGGGCTGCTCCCCGGAGCTGGGCTCCCAGAAG	2746
Qy	2613	AACAGATCATTACCTGGTTCCAGTTTCACAGCTACCTGCAGAGGCAGAGCGTCTCTGACC	2672
Db	2747	AACAGATCATTACCTGGTTCCAGTTTCACAGCTACCTGCAGAGGCAGAGCGTCTCTGACC	2806
Qy	2673	TGGAGAAGCACTTCACCCAGCTCACCAAGGAAGTGACACTCATCGAGGAGCTTCACTGTG	2732
Db	2807	TGGAGAAGCACTTCACCCAGCTCACCAAGGAAGTGACACTCATCGAGGAGCTTCACTGTG	2866
Qy	2733	CGGGACAGGCCAAGGTGGTCCGGAAGCTGCAGGGGAAGCGGCTGGGCCAGCTCCAGCCTC	2792
Db	2867	CGGGACAGGCCAAGGTGGTCCGGAAGCTGCAGGGGAAGCGGCTGGGCCAGCTCCAGCCTC	2926
Qy	2793	TGCCCCAGACCTTAAGAGCCTGGGCGCTGCTCCAGCTGGACGGCACTCCGAGGGTGTGCA	2852
Db	2927	TGCCCCAGACCTTAAGAGCCTGGGCGCTGCTCCAGCTGGACGGCACTCCGAGGGTGTGCA	2986
Qy	2853	GGGCGGCCAGCGCTCGCCTGGCTGGTGCAGTCAGGAACAGAAGCTTCCGGGAAAAGGCTT	2912
Db	2987	GGGCGGCCAGCGCTCGCCTGGCTGGTGCAGTCAGGAACAGAAGCTTCCGGGAAAAGGCTT	3046
Qy	2913	TGCTGTTCTACACCAACGCCCTGGCAGAGAACGACGCAAGGCTCCAGCAGGCCGCATGCC	2972
Db	3047	TGCTGTTCTACACCAACGCCCTGGCAGAGAACGACGCAAGGCTCCAGCAGGCCGCATGCC	3106
Qy	2973	TAGCGCTCAAACACCTCAAGGGCATTGAAAGCATCGACCAGACTGCCAGCCTGTGCCAGT	3032
Db	3107	TAGCGCTCAAACACCTCAAGGGCATTGAAAGCATCGACCAGACTGCCAGCCTGTGCCAGT	3166

Qy	3033	CTGACCTGGAGGCCGTGCGGGCGGCAGCCCGGGAAACCACACTGTCGTTTCGGTGAAAAAG	3092
Db	3167	CTGACCTGGAGGCCGTGCGGGCGGCAGCCCGGGAAACCACACTGTCGTTTCGGTGAAAAAG	3226
Qy	3093	GACGGTTAGCTTTTGTGAGAAGATGGACAAGCTCTGCTCAGAACAAAGAGAAGTCTTTTGCC	3152
Db	3227	GACGGTTAGCTTTTGTGAGAAGATGGACAAGCTCTGCTCAGAACAAAGAGAAGTCTTTTGCC	3286
Qy	3153	AGGAGGCAGATGTTGAAATCACAATATTTTAAAAAATCCTGGCTGATGAGCACAAATCTC	3212
Db	3287	AGGAGGCAGATGTTGAAATCACAATATTTTAAAAAATCCTGGCTGATGAGCACAAATCTC	3346
Qy	3213	ACATCGTTTTTTTTTGCTGCTGCCCAGCCTGGACATAGCCTGCACCTCTGGGTAATGGTGCT	3272
Db	3347	ACATCGTTTTTTTTTGCTGCTGCCCAGCCTGGACATAGCCTGCACCTCTGGGTAATGGTGCT	3406
Qy	3273	GTGCACCTCCTCCAGGAGTGTGAGCTGCCCAGAGCTCTACCTGAGACTCCGGCCATTGACC	3332
Db	3407	GTGCACCTCCTCCAGGAGTGTGAGCTGCCCAGAGCTCTACCTGAGACTCCGGCCATTGACC	3466
Qy	3333	CAGCCCCAGGGCATGGGCTGGTCTTTTGTACAGAGGCAGAAAAAGCAAGGCAAAGGTAC	3392
Db	3467	CAGCCCCAGGGCATGGGCTGGTCTTTTGTACAGAGGCAGAAAAAGCAAGGCAAAGGTAC	3526
Qy	3393	AGCATTCCAGGGGCTGCACGGCCTCAACAGAGCGCTCAACTTCTGGCTGAGGGTCTGTGT	3452
Db	3527	AGCATTCCAGGGGCTGCACGGCCTCAACAGAGCGCTCAACTTCTGGCTGAGGGTCTGTGT	3586
Qy	3453	GACCTTCCCCGAGATGCAGAGCTGAGCCAAACTAGGTGGCCACCTACAAAAGGGCCAAGG	3512
Db	3587	GACCTTCCCCGAGATGCAGAGCTGAGCCAAACTAGGTGGCCACCTACAAAAGGGCCAAGG	3646
Qy	3513	CCAGGCAAGTTGAGGCCCTAAATAAAAGGCTCCAAGGCAAGTGTGTAGAACTCCAGGCCCT	3572
Db	3647	CCAGGCAAGTTGAGGCCCTAAATAAAAGGCTCCAAGGCAAGTGTGTAGAACTCCAGGCCCT	3706
Qy	3573	CGCTGCCGGTCAGCTGCTCGGCACCTTCTGCGTCAAGAGGCACTGGGGATGCAGCAGGCTG	3632
Db	3707	CGCTGCCGGTCAGCTGCTCGGCACCTTCTGCGTCAAGAGGCACTGGGGATGCAGCAGGCTG	3766
Qy	3633	GCAGGTGGCTGGCCCTGCTAATGCAAGACTGCTCAGGCCATTTTCAGCAGCAGCCAGGTGT	3692
Db	3767	GCAGGTGGCTGGCCCTGCTAATGCAAGACTGCTCAGGCCATTTTCAGCAGCAGCCAGGTGT	3826
Qy	3693	CACCTTGGTGAGCTGGGGAAGGTGGGAAGGCACAAAGCCAGGGTTTCTACAACCACACTC	3752
Db	3827	CACCTTGGTGAGCTGGGGAAGGTGGGAAGGCACAAAGCCAGGGTTTCTACAACCACACTC	3886
Qy	3753	TCAGCCCGACTGACTTGCTGCGAGTGTGGTGGAGCTCACAGACGGCGGCTGGTGGATGG	3812
Db	3887	TCAGCCCGACTGACTTGCTGCGAGTGTGGTGGAGCTCACAGACGGCGGCTGGTGGATGG	3946
Qy	3813	TGGACTGTGAACCTCACTTTCCCTATGTTTCAGCAGCACAAAGGGAAGAAGCCACCACATC	3872
Db	3947	TGGACTGTGAACCTCACTTTCCCTATGTTTCAGCAGCACAAAGGGAAGAAGCCACCACATC	4006

Qy	3873	AGCCCAGGAGCCCTGAGCAGCACAGGCAGTAGGGCCACTCACTTTGGCCATCCGCACCCA	3932
Db	4007	AGCCCAGGAGCCCTGAGCAGCACAGGCAGTAGGGCCACTCACTTTGGCCATCCGCACCCA	4066
Qy	3933	AATGCAATCAATCAACCCAGCTTCGGAAGCTACCCCTAGGATCTCGTCAATAAACTGCTAA	3992
Db	4067	AATGCAATCAATCAACCCAGCTTCGGAAGCTACCCCTAGGATCTCGTCAATAAACTGCTAA	4126
Qy	3993	GAAGCCATCAACTGGCCTAAAGAAAGAGTTCACTGAAGAACGCAATTGCTTTAAAGAAAG	4052
Db	4127	GAAGCCATCAACTGGCCTAAAGAAAGAGTTCACTGAAGAACGCAATTGCTTTAAAGAAAG	4186
Qy	4053	AAAAATTAGTTTCCTATTTAAGTCTTAAAAAAAAGCAAACCATGTCCTGAGATGTCTGTG	4112
Db	4187	AAAAATTAGTTTCCTATTTAAGTCTTAAAAAAAAGCAAACCATGTCCTGAGATGTCTGTG	4246
Qy	4113	TTAATAGTGCAGAGAGAACCTAGGGTTTGAGGTTGCTGTAGCAATGGCATTGGAGAACTT	4172
Db	4247	TTAATAGTGCAGAGAGAACCTAGGGTTTGAGGTTGCTGTAGCAATGGCATTGGAGAACTT	4306
Qy	4173	TAACTTGAACATTCTCATCGATACTTCCTGGACATATTT	4211
Db	4307	TAACTTGAACATTCTCATCGATACTTCCTGGACATATTT	4345

Qy 572 ATCTTCGAAGCATTGAAAAGAGGCCTCAAGGAGTATCTGTGTGTGCAGCAGGCTGAGCTG 631
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
 Db 122 ATCTTCGAAGCATTGAAAAGAGGCCTCAAGGAGTATCTGTGTGTGCAGCAGGCTGAGCTG 181

 Qy 632 GACCACCTGTCTGGACGCCACAAAGACACCAGGAGGAATTCAGGCTGGCTTTCTATTAT 691
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
 Db 182 GACCACCTGTCTGGACGCCACAAAGACACCAGGAGGAATTCAGGCTGGCTTTCTATTAT 241

 Qy 692 GACCTGGACAAGCAAACGCGCTGTGTGGAAAGGCACATTCGGAAGATGGAGTTTCACATC 751
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
 Db 242 GACCTGGACAAGCAAACGCGCTGTGTGGAAAGGCACATTCGGAAGATGGAGTTTCACATC 301

 Qy 752 AGCAAGGTGGATGAGCTGTACGAGGACTACTGCATCCAGTGCCGCCTGCGCGACGGCGCC 811
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
 Db 302 AGCAAGGTGGATGAGCTGTACGAGGACTACTGCATCCAGTGCCGCCTGCGCGACGGCGCC 361

 Qy 812 TCCAGCATGCAGCGGGCCTTCGCCCCGGTGCCCCCGAGCCGCGCAGCCCCGAGAGAGCCTG 871
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
 Db 362 TCCAGCATGCAGCGGGCCTTCGCCCCGGTGCCCCCGAGCCGCGCAGCCCCGAGAGAGCCTG 421

 Qy 872 CAGGAGCTGGGCGCGAGCCTGCACGAGTGCGCCGAGGACATGTGGCTCATCGAGGGGGCC 931
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
 Db 422 CAGGAGCTGGGCGCGAGCCTGCACGAGTGCGCCGAGGACATGTGGCTCATCGAGGGGGCC 481

 Qy 932 CTGGAGGTTACCTGGGCGAGTTCCACATCAGGATGAAAGGCTTGGTGGGCTACGCACGC 991
 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
 Db 482 CTGGAGGTTACCTGGGCGAGTTCCACATCAGGATGAAAGGCTTGGGGGGCTACGCACGC 541

 Qy 992 CTCTGTCCCGGAGACCACTATGAGGTGCTCATGCGTCTGGG 1032
 ||||||||||||||||||||||||||||||||||||||||||||
 Db 542 CTCTGTCCCGGAGACCACTATGAGGTGCTCATGCGTCTGGG 582